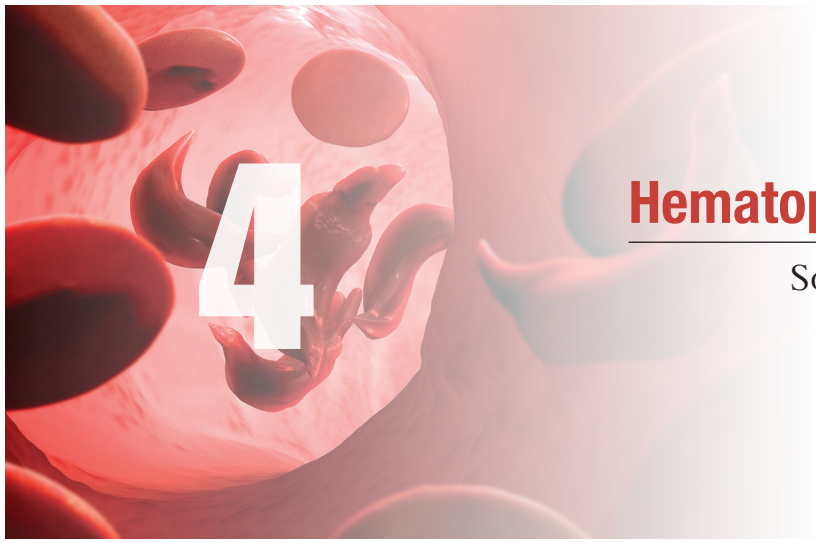

Hematopoietic growth factors

Sophie Park and Gerald A. Soff

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Introduction

The hematopoietic growth factors (HGFs) and their receptors play essential roles in regulating hematopoiesis. Specific factors for each hematopoietic lineage are critical for producing and maintaining normal circulating levels of the cells. Granulocyte colony-stimulating factor (G-CSF) regulates neutrophil production; granulocyte-macrophage colony-stimulating factor (GM-CSF) enhances production of neutrophils, monocytes, and eosinophils; erythropoietin (EPO) regulates red blood cell (RBC) production; and thrombopoietin (TPO) enhances platelet production. This chapter focuses on the results of clinical trials and approved uses for these HGFs.

Myeloid growth factors

Granulocyte colony-stimulating factor (filgrastim, tbo-filgrastim, and lenograstim)

G-CSF is a myeloid growth factor produced by a number of cell types including monocytes, macrophages, fibroblasts, and endothelial cells. G-CSF plays the central role of regulating neutrophil formation and deployment. In healthy individuals, circulating levels of G-CSF are low or undetectable. A dramatic increase in the circulating levels of G-CSF occurs in the setting of infection and inflammation and with the administration of endotoxin or mediators of inflammation, such as interleukin-1 and tumor necrosis factor.

The biological effects of G-CSF are mediated through the G-CSF receptor expressed on both mature neutrophils and neutrophil progenitors (see video in online edition). G-CSF knockout mice with a targeted disruption of the G-CSF receptor develop severe neutropenia, whereas hematocrit levels and platelet counts are normal. Mutations in the G-CSF receptor results in severe congenital neutropenia progressing to myelodysplasia or acute myeloid leukemia (AML) often have acquired mutations in the G-CSF receptor, most of which consist of truncation of the cytoplasmic tail of the receptor (see Chapter 19).

Available recombinant forms of G-CSF include filgrastim produced in *Escherichia coli* by the introduction of the human G-CSF gene. This form is identical to native human G-CSF except for the addition of an amino-terminal

The online version of this chapter contains an educational multimedia component on normal hematopoiesis.

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Off-label drug use: Sophie Park: deferasirox and lenalidomide in myelodysplastic syndromes. Gerald A. Soff: All discussion of thrombopoietin-related drugs is currently off-label.

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methionine. Filgrastim is licensed for use in the United States and in many other countries (Table 4-1). An alternative nonglycosylated recombinant methionyl form of G-CSF, tbo-filgrastim, has been approved by the US Food and Drug Administration (FDA) (Table 4-2). Lenograstim is a glycosylated form of G-CSF produced in a mammalian cell line and is not approved for clinical use in the United States.

Pegylated methionyl G-CSF (pegfilgrastim)

Pegfilgrastim is methionyl G-CSF with polyethylene glycol covalently bound to the amino-terminal methionine residue. Importantly, pegylation reduces the renal clearance of G-CSF through stearic hindrance and prolongs its circulation and the duration of its effects. Clinical trials comparing pegylated G-CSF and G-CSF demonstrated similar biological activities and clinical benefits, including the duration of chemotherapy-induced severe neutropenia and occurrence of febrile neutropenia (FN). The pharmacokinetics of pegfilgrastim should not be affected by hepatic insufficiency, but it has not been evaluated adequately in this setting. Although less studied in children, the efficacy and safety of pegfilgrastim appears similar to that in adults. The FDA-approved indications for pegfilgrastim are shown in Table 4-3.

On 6 March 2015, the FDA approved the first biosimilar compound: filgrastim-sndz (Zarxio; Sandoz). Biosimilars have the same amino acid sequence as the original compound and are intended to reduce the price of the medication. Filgrastim-sndz was approved on the basis of pharmacologic data showing equivalent pharmacokinetics and pharmacodynamics to filgrastim, as well as a clinical trial in human subjects which showed no clinically meaningful difference in the rate of FN between filgrastim and filgrastim-sndz.

Table 4-1 FDA-approved indications for filgrastim

Accelerate neutrophil recovery in patients receiving myelosuppressive chemotherapy
Accelerate neutrophil recovery after acute myeloid leukemia induction or consolidation chemotherapy
Accelerate neutrophil recovery in patients following a bone marrow transplant
Mobilize peripheral blood stem cells
Severe chronic neutropenia (idiopathic, cyclic, congenital)

Table 4-2 FDA-approved indication for tbo-filgrastim

Reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia

Table 4-3 FDA-approved indication for pegfilgrastim

Decrease the incidence of infection as manifested by febrile neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia

Granulocyte-macrophage colony-stimulating factor (sargramostim, molgramostim)

GM-CSF is a glycoprotein constitutively produced by monocytes, macrophages, endothelial cells, and fibroblasts. GM-CSF production is enhanced by inflammatory cytokines such as interleukin-1 or tumor necrosis factor. GM-CSF promotes the growth of myeloid colony-forming cells, increases the number of circulating neutrophils and monocytes, and enhances the phagocytic function and microbicidal capacity of mature myeloid cells. GM-CSF also stimulates dendritic cell maturation, proliferation, and function, and it increases antigen presentation by macrophages and dendritic cells. That GM-CSF is not essential for hematopoiesis and this is confirmed by the demonstration of normal complete blood counts and normal number of marrow progenitor cells in GM-CSF knockout mice. Evidence exists, however, that GM-CSF plays a key role in the function of pulmonary macrophages. Mice that lack GM-CSF have lung pathology consistent with pulmonary alveolar proteinosis. Similarly, some cases of human pulmonary alveolar proteinosis are related to a defect in the common β-chain of the receptor for GM-CSF, IL-3, and IL-5. Infants that are so affected have decreased alveolar macrophage function and accumulate surfactant in the alveoli.

Recombinant forms of GM-CSF available for clinical use include sargramostim derived from yeast and molgramostim expressed by *E. coli*. The sequence of sargramostim differs from that of native GM-CSF by a single amino-acid substitution at position 23. Only sargramostim is approved for clinical use by the FDA (Table 4-4).

Clinical use of G-CSF and GM-CSF

Prevention of chemotherapy-induced febrile neutropenia

The main clinical use of G-CSF and GM-CSF is for the prevention of FN (temperature >38.3°C with neutrophils less than 0.5×10^9/L) in patients receiving cancer chemotherapy. FN represents the major dose-limiting toxicity of cancer chemotherapy and is associated with considerable morbidity, mortality, and costs. The clinical use of G-CSF is based on results of numerous randomized controlled trials and meta-analyses of such trials and

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Table 4-4 FDA-approved indications for GM-CSF sargramostim

Reduce the risk of death due to infection in patients ≥55 years undergoing induction chemotherapy for acute myeloid leukemia
Mobilize autologous peripheral blood stem cells and enhance neutrophil recovery after transplantation
Promote neutrophil recovery after autologous or allogeneic bone marrow transplantation
Improve neutrophil production in patients with delayed engraftment or graft failure after autologous or allogeneic bone marrow transplantation

supported by clinical practice guidelines. FDA approval of G-CSF for prevention of FN was based on 2 pivotal randomized controlled trials in patients with small-cell lung cancer receiving intensive combination chemotherapy associated with prolonged severe neutropenia with a high risk of FN. Primary prophylaxis with G-CSF initiated within the first 3 days after chemotherapy and continued for up to 10 days reduced the duration of severe neutropenia to about 3 days and reduced the occurrence of FN and documented infection by 50%. A pivotal randomized trial in patients with breast cancer found tbo-filgrastim to be superior to placebo, and equivalent to filgrastim, in duration of severe neutropenia after chemotherapy.

The results of these trials have been confirmed in multiple other randomized controlled trials across a spectrum of malignancies and chemotherapy regimens, consistently demonstrating a reduction in the risk of FN in the initial cycle, as well as across repeated cycles of treatment. At the same time, little or no benefit from G-CSF administration has been observed when treatment is delayed until neutropenia is already present. Although individual studies were not sufficiently powered to assess any impact on infection-related or all-cause mortality, meta-analyses of these trials have demonstrated a significant reduction in these complications with primary G-CSF prophylaxis in patients receiving conventional chemotherapy. These analyses also have demonstrated that G-CSF prophylaxis enables a greater percentage of patients to receive full-dose chemotherapy on schedule through the avoidance of neutropenic complications that lead to preemptive dose reductions or treatment delays. Meta-analyses of randomized controlled trials also suggest that G-CSF support of patients receiving cancer chemotherapy may improve long-term outcomes, including survival, presumably most notably in patients treated with curative intent.

Pegfilgrastim for prevention of febrile neutropenia

A randomized phase 3 double-blind, placebo-controlled clinical trial of primary prophylaxis with pegfilgrastim was conducted in patients with breast cancer receiving docetaxel 100 mg/m^2 every 3 weeks to determine the efficacy of pegfilgrastim when given with less myelosuppressive regimens. Patients were randomly assigned to pegfilgrastim 6 mg or placebo on the day following chemotherapy. Patients in the pegfilgrastim arm experienced significantly lower incidence of FN (1% versus 17%), hospitalizations (1% versus 14%) and anti-infective use (2% versus 10%) (all $P < 0.001$). Pegfilgrastim is FDA approved to reduce the risk of FN in patients undergoing chemotherapy with a 17% or greater risk of FN without growth factor support (Table 4-3).

On the basis of the prolonged half-life of pegfilgrastim, it has been recommended that chemotherapy not be given sooner than 14 days after a dose of pegfilgrastim. Considerable experience with pegfilgrastim in support of every 2-week chemotherapy schedules, however, has demonstrated acceptable efficacy and safety. Otherwise, the safety profile of pegfilgrastim is similar to that of other forms of G-CSF.

GM-CSF for prevention of febrile neutropenia

GM-CSF is approved to reduce the risk of death from infections in patients ≥55 years old undergoing induction therapy for AML (Table 4-4). There is limited evidence from randomized trials for the use of GM-CSF in non-myeloid malignancies, and it is not FDA approved for the prevention of FN in this population.

Clinical guidelines for the use of myeloid growth factors

The American Society of Clinical Oncology (ASCO), the National Comprehensive Cancer Network, and other organizations have developed guidelines for the use of myeloid growth factors to prevent FN. In brief, current ASCO guidelines (Table 4-5) include the following:

1. Primary prophylaxis is recommended for patients at high risk (>20%) of FN due to age, medical history, disease characteristics, or the myelotoxicity of the chemotherapy regimen.
2. Primary prophylaxis should be given with "dose-dense" chemotherapy regimens.
3. Secondary prophylaxis after a neutropenia-related event has occurred generally is recommended if reduced dosing or dose intensity will compromise disease-free or overall survival or expected treatment outcome.

Specific factors predisposing to FN and serving as current indications to consider the use of myeloid growth factors are listed in Table 4-6.

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Table 4-5 American Society of Clinical Oncology guidelines for use of myeloid growth factors to prevent FN

Setting/indication	Recommended	Not recommended
General circumstances	FN risk in the range of 20% or higher	
Special circumstances	Clinical factors dictate use	
Secondary prophylaxis	Based on chemotherapy reaction among other factors	
Therapy of afebrile neutropenia		Routine use
Therapy of febrile neutropenia	If high-risk for complications or poor clinical outcomes	Routine use
AML	Following induction therapy, patients >55 years old most likely to benefit	Priming prior to cytotoxic chemotherapy outside a clinical trial
	After the completion of consolidation chemotherapy	
MDS		Routine use in neutropenic patients
Acute lymphocytic leukemia	After the completion of initial chemotherapy or first postremission course	
Radiotherapy	Consider if receiving radiation therapy alone and prolonged delays are expected	Patients receiving concurrent chemotherapy and radiation
Older patients	If ≥65 years old with diffuse aggressive NHL and treated with curative chemotherapy	
Pediatric population	Primary prophylaxis of pediatric patients with a likelihood of FN and the secondary prophylaxis or therapy for high-risk patients	G-CSF use in children with ALL

Adapted from Smith TJ et al, *J Clin Oncol*. 2015;33(28):3199-212, with permission.

NHL, non-Hodgkin lymphoma.

Treatment for febrile neutropenia

All patients with FN should be treated empirically with antibiotics after a thorough physical examination directed at identifying a site of infection and after appropriate cultures are obtained. A number of studies have addressed whether patients with FN benefit from initiation of a myeloid growth factor in addition to broad-spectrum antibiotics. A meta-analysis of 13 randomized clinical trials compared the use of G-CSF or GM-CSF plus antibiotics with the use of antibiotics alone in patients with chemotherapy-induced FN. The meta-analysis showed that the use of a myeloid growth factor accelerated the time to neutrophil recovery and shortened hospital stay but did not affect overall survival. ASCO guidelines recommend that the myeloid growth factors should not be used routinely as adjuncts to antibiotics for patients with FN. These guidelines recommend that the myeloid growth factors should be considered for patients expected to have prolonged (>10 days) and profound neutropenia ($<0.1 \times 10^9$/L); use also should be considered for those >65 years old with pneumonia, hypotension, invasive fungal infections, or sepsis.

Table 4-6 Risk factors for chemotherapy-associated neutropenia and its complications

Age >65 years
Previous chemotherapy or radiation therapy
Bone marrow involvement of tumor
Preexisting neutropenia, infections, open wounds, or recent surgery
Poor performance status
Decreased renal function
Decreased liver function, particularly increased bilirubin level

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Acute myeloid leukemia

Neutropenia, anemia, and thrombocytopenia are common presenting features of AML and also are important complications in its treatment. There are many studies of the use of myeloid growth factors to sensitize leukemic cells to increase the effectiveness of chemotherapy and prevent infectious complications. Although G-CSF and GM-CSF may shorten the duration of neutropenia during the induction phase of chemotherapy, neither consistently reduces the occurrence of FN, infections, or the duration of hospitalization. Results for sensitization of the leukemic cells to chemotherapy also are inconsistent, and use of the myeloid growth factors in this way is not recommended except for research studies.

During the consolidation phase of treatment, the marrow is more responsive, and 2 large randomized trials have demonstrated significant decreases in the duration of severe neutropenia with an associated decrease in infections

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requiring antibiotics with G-CSF therapy. No consistent favorable or detrimental impact of G-CSF or GM-CSF on treatment response and survival has been observed.

Acute lymphoblastic leukemia

Neutropenia is a common consequence of treatment in patients with acute lymphoblastic leukemia (ALL). Eight randomized controlled trials, including more than 700 adults and children, demonstrated that neutrophil recovery is accelerated with myeloid growth factor therapy, mostly utilizing G-CSF. No consistent therapeutic benefits in reducing infections, shortening hospitalizations, or improving the overall treatment outcomes were observed.

Mobilization of autologous peripheral blood stem cells and enhancement of neutrophil recovery after autologous transplantation

Autologous peripheral blood stem cells are collected routinely from cancer patients by leukapheresis after cytoreductive chemotherapy or after cytoreductive chemotherapy followed by G-CSF or GM-CSF. Mobilization with G-CSF has been demonstrated to involve several steps. First, G-CSF markedly enhances neutrophil production. G-CSF administration also releases neutrophil elastase and cathepsin G from the granules of the developing marrow neutrophils. When released, these proteases cleave adhesion molecules expressed on the surfaces of the marrow stromal cells. Cleavage of the bond of chemokine receptor 4 (CXCR4), expressed on hematopoietic progenitor cells, and its ligand chemokine ligand 12 (CXCL12, also known as stromal cell–derived factor 1 or SDF-1), expressed on marrow stromal cells, is thought to be the principal mechanism for progenitor cell release into the circulation.

As discussed in Chapter 14, transplantation of autologous peripheral blood stem cells results in the restoration of hematopoiesis after high-dose (myeloablative) chemotherapy. Clinical trials of autologous peripheral blood stem cell transplantation have shown that the use of a myeloid cytokine after stem cell infusion accelerates neutrophil recovery by 2 to 4 days. However, neutrophil recovery to $>0.5 \times 10^9$/L is so rapid (median 11 to 14 days) without a myeloid growth factor that it has been difficult to demonstrate a meaningful clinical benefit of G-CSF or GM-CSF, including reduced risk of sepsis or death due to infection in patients receiving a peripheral blood stem cell product. Therefore, consensus on their use in this setting is lacking. A few randomized studies have found no difference in safety of pegfilgrastim as compared to filgrastim in this setting. Plerixafor, a CXCR4 antagonist, acts synergistically with G-CSF to yield greater numbers of $CD34^+$ stem cells and is FDA approved as an adjunct to G-CSF for stem cell mobilization in certain conditions, particularly for patients who are expected to mobilize poorly with G-CSF (age >60 years, use of fludarabine or lenalidomide or number of previous chemotherapies).

Mobilization of peripheral blood stem cells from normal donors for allogeneic transplantation

G-CSF treatment of normal donors effectively mobilizes stem cells for use in subsequent allogeneic transplantation and has an excellent safety profile.

Acceleration of neutrophil recovery after bone marrow and umbilical cord blood transplantation

Peripheral blood stem cells are preferred over bone marrow in some instances because of the ease of collection of peripheral blood stem cells, lower risk of primary graft failure, and a more rapid neutrophil and platelet recovery. Nonetheless, bone marrow is preferred for many recipients as the risk of graft-versus-host disease is lower. When bone marrow transplantation is performed, a myeloid growth factor after bone marrow stem cell infusion significantly accelerates neutrophil recovery by approximately 4 to 5 days. A meta-analysis of 18 clinical trials totaling 1,198 patients showed no change in the risk of acute or chronic graft-versus-host disease after allogeneic stem cell transplantation with G-CSF when compared with patients who did not receive a myeloid growth factor.

Umbilical cord blood transplants have been able to extend the benefits of allogeneic transplant to those without a matched donor. As a result of the size and composition of the graft, hematopoietic recovery is prolonged, and recipients are at a higher risk for infectious complications. In retrospective studies, the use of G-CSF reduced the time to neutrophil recovery by approximately 10 days. Although prospective data are lacking, G-CSF is routinely used after cord blood transplant.

Improvement of neutrophil production in patients with delayed engraftment or graft failure after bone marrow transplantation

Patients who do not achieve a neutrophil count of 0.1×10^9/L by day 21 after transplantation or whose neutrophil count drops below 0.5×10^9/L following engraftment in the absence of relapse often respond to a myeloid growth factor with improvement in neutrophil production.

Severe chronic neutropenia (idiopathic, cyclic, congenital)

Severe chronic neutropenia is a heterogeneous group of inherited and acquired disorders characterized by a

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persistent neutrophil count of $<0.5 \times 10^9$/L and recurrent bacterial infections, including Kostmann syndrome, sporadic and autosomal dominant severe congenital neutropenia, and cyclic neutropenia (see Chapter 15).

Most patients with congenital and cyclic neutropenia respond well to treatment with G-CSF. Treatment significantly improves neutrophil counts, dramatically decreases the incidence and severity of bacterial infections, and appears to improve survival. Responses can be maintained over many years with daily or alternate day G-CSF. Patients with cyclic neutropenia maintained on G-CSF continue to have regular fluctuations in the neutrophil count, but the depth of the nadir is reduced and lasts for fewer days. Patients with severe congenital neutropenia attributable to mutations in *ELANE*, *HAX1*, or *WAS* or as-yet-unknown mutations are at risk of developing AML. The lifetime risk is estimated to be as high as 30%. In contrast, there is no apparent risk of AML in patients with cyclic neutropenia. There is no strong evidence to suggest that G-CSF use in severe congenital neutropenias increases leukemia risk.

The Severe Chronic Neutropenia International Registry is a useful source for additional information about the diagnosis and treatment of severe chronic neutropenia (http://depts.washington.edu/registry/).

Myelodysplasia

The myelodysplastic syndromes (MDS), also discussed in Chapter 18, are a group of acquired neoplastic hematopoietic stem cell disorders with the hallmark of ineffective hematopoiesis. Both quantitative and qualitative defects in neutrophils impair the ability to ward off bacterial infection in these patients. A handful of clinical trials have investigated treatment of MDS with HGFs. Treatment with G-CSF can normalize the neutrophil count in patients with MDS, but whether this translates into reduced mortality from bacterial or fungal infection is less clear. A randomized, phase 3 trial of 102 patients with high-risk MDS did not demonstrate a reduction in infectious complication but suggested an increase in nonleukemic disease-related deaths associated with the routine use of G-CSF to increase neutrophil counts. There is no convincing evidence at present that growth factor therapy accelerates progression from low-risk MDS to AML.

Other potential clinical uses of G-CSF

HIV

Neutropenia is common in HIV infection and is found in 5% to 10% and 50% to 70% of patients with early and advanced disease, respectively. Furthermore, medications used in the management of HIV, associated opportunistic infections, and malignancies can lead to neutropenia. Treatment with G-CSF promptly increases the neutrophil count to the normal range in most patients. A large multicenter trial that randomized 258 HIV-positive patients with a low CD4 count (0.2×10^9/L) and absolute neutrophil count of 0.75×10^9 to 1.0×10^9/L showed that G-CSF–treated patients (dose adjusted to increase the absolute neutrophil count to 2.0×10^9 to 10.0×10^9/L) had fewer bacterial infections, less antibiotic use, and fewer hospital days, but no change in viral load, in comparison with the control group.

Leukapheresis

Large numbers of neutrophils can be collected by leukapheresis from normal donors pretreated with G-CSF plus dexamethasone, and these neutrophils exhibit normal function in vitro. Transfusion of G-CSF–stimulated neutrophil leukapheresis products into severely neutropenic leukemia patients or stem cell transplant recipients can transiently raise the peripheral neutrophil count to the normal range ($<2.0 \times 10^9$/L). Whether neutrophil transfusions increase survival in patients with profound sustained neutropenia who have an active bacterial or fungal infection is under investigation.

Pneumonia

A number of clinical trials have explored the use of G-CSF in nonneutropenic adults with community-acquired pneumonia or hospital-acquired pneumonia. In an evidence-based review, 6 studies with a total of 1,984 people were identified. G-CSF use appeared to be safe, with no increase in the incidence of serious adverse events. The use of G-CSF, however, was not associated with improvement in mortality at 28 days.

Myocardial infarction

Studies have suggested that stem cells mobilized from the marrow by myeloid growth factor may improve cardiac function following myocardial infarction, presumably by stimulating angiogenesis. However, a recent meta-analysis of 7 trials involving 354 patients who received myeloid growth factor or placebo for 4 to 6 days after acute myocardial infarction found no difference in mortality and no improvement in parameters of left ventricular function.

In 1 small prospective clinical study, G-CSF therapy with intracoronary infusion of peripheral blood stem cells showed improved cardiac function and promoted angiogenesis in patients with myocardial infarction. Aggravation of in-stent restenosis led to early termination of the study. Although studies such as these are intriguing for the

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utilization of G-CSF–mobilized stem cells for a variety of new applications, no conclusive evidence exists at present supporting these applications.

Side effects of G-CSF

The major side effect of G-CSF is bone pain in the hips, which usually coincides with marrow recovery and may be due to the expansion of hematopoiesis within the marrow cavity. Medullary bone pain occurs in approximately 30% of patients treated with G-CSF, and osteoporosis has been observed in some patients who were administered G-CSF. Other side effects of G-CSF include headache and fatigue. G-CSF should not be used in patients with sickle cell disease; case reports document the precipitation of sickling and severe pain crisis in these individuals. Other rare side effects include splenic rupture and adult respiratory distress syndrome.

Side effects of GM-CSF

The major side effect of GM-CSF is a flu-like illness characterized by fever (22% of patients) and myalgias and arthralgias (15%). A fraction of patients treated with GM-CSF experience fluid retention (8%) or dyspnea (13%). GM-CSF should not be used concurrently with chemoradiotherapy.

Risk of leukemia with G-CSF and GM-CSF

Concerns have been expressed that G-CSF and GM-CSF might cause leukemia as they are known to stimulate proliferation of leukemic blasts. At present there is no convincing evidence that treatment outcomes for AML are worsened by myeloid growth factor treatments used in conjunction with appropriate chemotherapy. In patients receiving myelotoxic chemotherapy agents for other types of cancer, there is a significant risk of secondary leukemias. This risk probably is related directly to specific leukemogenic chemotherapy agents and regimens. Recent analysis of data from randomized trials suggests that the risk of AML may be increased in those receiving chemotherapy supported by the myeloid growth factors, but interpretation of the results is made difficult by the observation that myeloid growth factor–treated patients usually receive larger doses and longer courses of chemotherapy. The long-term risk of leukemia is also of importance to normal stem cell donors, but little information exists regarding donors mobilized with myeloid growth factors. It is estimated that it will require the observation of a little over 2,000 donors for a minimum of 10 years to detect a 10-fold increase in the incidence of leukemia. However, it is important to note that patients with idiopathic or cyclic neutropenia have received G-CSF for many years without progression to leukemia.

New formulations of G-CSF

Because of the potency and effectiveness of G-CSF, there have been many efforts to identify additional myeloid growth factors and make new derivatives from the parent molecules. Several new products with a prolonged duration of their stimulatory effects, similar to pegylated G-CSF, are in development. A key issue is whether or not the new molecules are immunogenic. The development of antibodies to a growth factor can be hazardous, as they can block the activity of the administered drug and also neutralize the effects of the naturally produced, endogenous growth factors, thus worsening neutropenia.

The number of laboratories and biopharmaceutical companies producing myeloid growth factors is also rapidly increasing. Their products are molecularly similar to the approved products and are called "biosimilars." Testing and introduction of biosimilars is proceeding rapidly with the first application for a biosimilar filgrastim being accepted by the FDA in mid-2014.

Erythroid growth factors

Erythropoietin

EPO is the principal HGF that regulates red blood cell production. The liver is the primary site of EPO production during fetal development. In adults, EPO production is predominantly by the juxtatubular interstitial cells of the renal cortex. The juxtatubular interstitial cells sense oxygen levels through an oxygen-dependent prolyl hydroxylase. With low oxygen tension, the half-life and function of hypoxia-inducible factor 1α (HIF-1α) is increased and drives production of erythropoietin. Plasma EPO levels are measurable by a clinically available enzyme-linked immunosorbent assay. In some patients with nonrenal anemia, the degree of plasma EPO elevation may assist in predicting response likelihood to recombinant human EPO (rhEPO) therapy.

EPO exerts its erythropoietic action by binding to its specific high-affinity cell surface receptor (EPOR) expressed on erythroid progenitor and precursor cells in the bone marrow (see video in online edition). EPOR does not possess intrinsic tyrosine kinase enzymatic activity. Its intracellular domain associates with a cytoplasmic tyrosine kinase, Janus kinase 2 (JAK2), to activate downstream signaling that promotes the proliferation, survival, and differentiation of erythroid cells. Low levels of EPOR expression have been found in neural tissues, endothelial cells, and other nonhematopoietic cell types. Targeted disruption of the genes encoding either EPO or EPOR in mice leads to severe in-utero anemia and embryonic

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death. Cardiovascular and neural abnormalities also have been reported. These mice exhibit normal formation of early and late erythroid progenitors, burst-forming unit–erythroid and colony-forming unit–erythroid, indicating that commitment to erythroid lineage does not require EPO but rather that terminal differentiation of colony-forming unit–erythroid into mature red blood cells depends on intact EPOR signaling.

Naturally occurring, dominant gain-of-function *EPOR* gene mutations that disrupt downregulation of JAK2 activation are associated with primary familial and congenital polycythemia. An acquired, somatic, activating *JAK2* V617F mutation is encountered in 95% of polycythemia vera cases and in about 50% of patients with other BCR-ABL1–negative myeloproliferative neoplasms. Mutations in the genes encoding HIF, von Hippel-Lindau proteins, and prolyl hydroxylase domain enzymes that regulate renal oxygen sensing and EPO production are found in some patients with secondary familial and congenital polycythemia due to inappropriate elevation of plasma EPO levels.

Recombinant human erythropoietins

Three main rhEPO preparations—epoetin alfa, epoetin beta, and darbepoetin alfa—are available for clinical use in the United States and Europe. The biologic activity and adverse effect profiles of these agents are comparable. The difference in the amount of posttranslational glycosylation of each product modulates the pharmacokinetic properties. These agents are produced by recombinant DNA technology, by a mammalian cell line into which the *EPO* gene has been introduced. Biosimilar products ("follow-on biologics") for epoetins have been available in some countries as the patent and exclusivity rights have expired.

Epoetin alfa was the first recombinant product approved by the FDA in 1989 for its indication in chronic kidney disease (CKD) patients, followed by its approval in 1993 in the oncology supportive care setting for chemotherapy-induced anemia (Table 4-7).

Table 4-7 FDA-approved indications for epoetin alfa

Anemia due to:
Chronic kidney disease in patients on dialysis and not on dialysis
The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of an additional 2 months of planned chemotherapy
Zidovudine in HIV-infected patients, and for reduction of allogeneic red cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery

Table 4-8 FDA-approved indications for darbepoetin alfa

Anemia due to:
Chronic kidney disease in patients on dialysis and patients not on dialysis
The effects of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of an additional 2 months of planned chemotherapy

Epoetin beta is available for clinical use in Europe. Darbepoetin alfa is a hyperglycosylated form and binds to the same cellular receptor. The modification of 2 additional N-linked oligosaccharide chains compared with EPO leads to a higher molecular weight than EPO and a threefold longer half-life in vivo. The advantage is that it can be administered less frequently than epoetin alfa or epoetin beta to achieve a comparable increment in hemoglobin (HgB). Darbepoetin alfa was approved by the FDA for clinical use in 2001 (Table 4-8).

Continuous erythropoietin receptor activator (CERA) is a structurally distinct pegylated epoetin beta product containing a methoxy polyethylene glycol polymer. This modification extends its half-life, allowing the dosing intervals to be prolonged up to once every 4 weeks to maintain hemoglobin levels in CKD patients on dialysis. CERA is approved for use in some European countries, as well as by the FDA. A long-acting CERA, called Mircera, is used commonly to treat the anemia associated with CKD and in dialysis patients.

FDA-approved clinical uses of rhEPO

Chronic kidney disease

Normocytic, normochromic anemia associated with EPO deficiency occurs in the majority of patients with CKD during progression to end-stage renal disease. Anemia contributes to CKD-related symptoms and has been associated with the presence of cardiac comorbidities, reduced quality of life, and increased risk of mortality. In patients with anemia due to CKD, rhEPO therapy improves hemoglobin levels and eliminates transfusion requirements; however, studies have shown that targeting and maintaining near-normal or normal hemoglobin levels is associated with increased morbidity and mortality risk.

Following a safety review in 2011, the FDA mandated changes to the drug labels for epoetin alfa and darbepoetin alfa, warning that in controlled trials patients experienced greater risks of death, serious adverse cardiovascular reactions, and stroke when they were administered rhEPO to target a hemoglobin level >11 g/dL. It was noted that no trial has identified a hemoglobin target level, rhEPO dose, or dosing strategy that does not increase these risks.

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Effective 24 June 2011, the FDA safety announcement indicated the following:

- Consider starting rhEPO treatment when hemoglobin level is <10 g/dL, without specifying how far below 10 g/dL is appropriate for an individual to initiate therapy. It is recommended to individualize dosing and use the lowest dose sufficient to reduce the need for red blood cell transfusions. A target hemoglobin level is not specified.
- For patients with CKD not on dialysis, consider initiating rhEPO treatment only when hemoglobin level is <10 g/dL and if the rate of hemoglobin decline indicates the likelihood of requiring a red blood cell transfusion and reducing alloimmunization or other transfusion-related risks is a goal. If the hemoglobin level exceeds 10 g/dL, reduce or interrupt rhEPO dose and use the lowest dose sufficient to reduce the need for transfusions.
- For patients with CKD on dialysis, initiate rhEPO treatment when hemoglobin is <10 g/dL. If the hemoglobin level approaches or exceeds 11 g/dL, reduce or interrupt the dose of rhEPO.
- For patients who do not respond adequately over a 12-week escalation period, increasing the rhEPO dose further is unlikely to improve response and may increase risks.

The initial dose of epoetin alfa in predialysis CKD patients is typically 50 to 100 U/kg administered subcutaneously once a week. Most patients respond to a regimen of 10,000 U/week. Darbepoetin alfa 60 mg every 2 weeks subcutaneously is an alternative regimen in predialysis patients.

For hemodialysis patients, the recommended initial dose of epoetin alfa is 50 to 100 U/kg 3 times per week. The weekly epoetin dose requirement was shown to be about 30% less with subcutaneous administration as compared with intravenous route in a randomized trial involving patients on hemodialysis. Most hemodialysis patients, however, receive epoetin alfa intravenously because of discomfort with subcutaneous injections and the convenience of an intravenous route during dialysis. Darbepoetin alfa typically is started at 0.45 mg/kg administered intravenously once a week.

Before and during rhEPO therapy, iron stores are assessed and monitored to avoid development of iron deficiency and to achieve maximum benefit from rhEPO. Ferritin levels typically are maintained at ≥100 ng/dL and the transferrin saturation at 20%. Many hemodialysis patients require intravenous iron infusions to ensure the adequacy of iron stores during rhEPO therapy.

Cancer patients receiving myelosuppressive chemotherapy

Patients with nonmyeloid malignancies receiving myelosuppressive chemotherapy frequently develop mild to moderate anemia. To ameliorate cancer- or chemotherapy-induced anemia and its associated symptoms such as fatigue, about 50% of patients require red blood cell transfusions during the course of their illness. In this clinical setting, epoetin alfa and darbepoetin alfa exhibit efficacy in increasing hemoglobin and reducing the requirement for red blood cell transfusions during chemotherapy. In a series of 9 meta-analyses, the relative risk for transfusion ranged from 0.58 to 0.67 in rhEPO-treated patients. Although the risks associated with allogeneic transfusions are avoided in some patients treated with rhEPO, the requirement for transfusions is not completely eliminated.

Several clinical trials and meta-analyses have reported that rhEPO therapy for chemotherapy-induced anemia may improve quality of life as measured by Functional Assessment of Cancer Therapy instruments. More recently, the presence, magnitude, and clinical significance of any potential beneficial effect of rhEPO on quality of life has been controversial, especially in the context of the accumulating evidence of risks of rhEPO therapy in this patient population, leading to use restrictions to minimize the potential for harm.

In 2008, the FDA mandated changes to the labels of epoetin alfa and darbepoetin alfa based on risks of shortened survival or increased risk of tumor progression in cancer patients, as well as the risks of cardiovascular complications reported in other studies. Starting in 2010, prescribers and hospitals had to enroll in and comply with the REMS (risk evaluation and mitigation strategy) program, termed the ESA APPRISE Oncology Program (Assisting Providers and Cancer Patients with Risk Information for the Safe Use of Erythropoiesis-Stimulating Agents) to prescribe or dispense rhEPO products to patients with cancer. Over the ensuing 5 years, the use of erythroid stimulating agents, especially in the setting of chemotherapy-induced anemia, dropped substantially. The REMS program stopped in 2017. The FDA-approved label for rhEPOs currently recommends the following:

- Use the lowest dose needed to avoid red blood cell transfusions.
- Use rhEPO only for anemia from myelosuppressive chemotherapy.
- rhEPO is not indicated for patients receiving myelosuppressive chemotherapy when the anticipated outcome is cure. The specific types of malignancies were not indicated.

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- Initiate rhEPO only if hemoglobin is <10 g/dL, and if there is a minimum of an additional 2 months of planned chemotherapy.
- Reduce dose by 25% if hemoglobin increases >1 g/dL in any 2-week period or if hemoglobin reaches a level at which transfusion is not required.
- Withhold dose if hemoglobin exceeds a level needed to avoid red cell transfusion.
- Discontinue use if there is no hemoglobin response or if transfusions are still required after 8 weeks of therapy.
- Discontinue following the completion of a chemotherapy course.

The typical starting dose of epoetin alfa is 150 U/kg subcutaneously 3 times per week, or 40,000 U subcutaneously weekly until completion of a chemotherapy course. The starting dose for darbepoetin alfa is 2.25 μg/kg/week or 500 μg every 3 weeks subcutaneously until completion of a chemotherapy course. An alternative darbepoetin regimen is 200 μg every 2 weeks with comparable efficacy to epoetin alfa 40,000 U weekly. Hemoglobin level is monitored weekly until stable. Previous studies have not identified a specific plasma endogenous EPO level above which patients would be less likely to respond to rhEPO therapy, though the higher the baseline EPO level, the less likely there will be a response to exogenous EPO.

Iron stores should be assessed before initiation of therapy and monitored periodically during therapy. Oral or parenteral iron supplementation may be required in some patients to maximize response to rhEPO. In patients who fail to respond to rhEPO, considerations include concomitant iron deficiency, blood loss, vitamin deficiencies (B_{12} and folate), hemolysis, anemia associated with the malignancy ("anemia of cancer"), or an underlying hematologic disorder.

American Society of Hematology/American Society of Clinical Oncology clinical practice guidelines

The American Society of Hematology (ASH)/American Society of Clinical Oncology (ASCO) Update Committee reviewed data published between January 2010 and May 2018 and presented the following recommendations for clinicians treating patients undergoing myelosuppressive chemotherapy who have a hemoglobin level <10 g/dL.

- Depending on clinical circumstances, erythropoiesis-stimulating agents (ESAs) may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin has declined to 10 g/dL. Red blood cell transfusion is also an option, depending on the severity of the anemia or clinical circumstances.
- ESAs should not be offered to patients with chemotherapy-associated anemia whose cancer treatment is curative in intent. ESAs should not be offered to most patients with nonchemotherapy-associated anemia.
- ESAs may be offered to patients with lower-risk myelodysplastic syndromes and a serum erythropoietin level <500 IU/L. In patients with myeloma, non-Hodgkin lymphoma, or chronic lymphocytic leukemia, clinicians should observe the hematologic response to cancer treatment before considering an ESA.
- Particular caution should be exercised in the use of ESAs concomitant with treatment strategies and diseases where the risk of thromboembolic complications is increased. In all cases, blood transfusion is a treatment option that should be considered.
- Before offering an ESA, clinicians should conduct an appropriate history, physical examination, and diagnostic tests to identify alternative causes of anemia aside from chemotherapy or an underlying hematopoietic malignancy. Such causes should be appropriately addressed before considering the use of ESAs.
- The Expert Panel considers epoetin beta and alfa, darbepoetin, and biosimilar epoetin alfa to be equivalent with respect to effectiveness and safety.
- ESAs increase the risk of thromboembolism, and clinicians should carefully weigh the risks of thromboembolism and use caution and clinical judgment when considering use of these agents.
- Hemoglobin may be increased to the lowest concentration needed to avoid or reduce the need for RBC transfusions, which may vary by patient and condition.
- ESAs should be discontinued in patients who do not respond within 6 to 8 weeks. Patients who do not respond to ESA treatment should be reevaluated for underlying tumor progression, iron deficiency, or other etiologies for anemia.
- Iron replacement may be used to improve hemoglobin response and reduce RBC transfusions for patients receiving ESA with or without iron deficiency. Baseline and periodic monitoring of iron, total iron-binding capacity, transferrin saturation, or ferritin levels is recommended.

Anemia associated with HIV infection

The prevalence and severity of anemia in patients with HIV disease have decreased in the era of highly active antiretroviral therapy. In a cohort of 9,690 patients, anemia (hemoglobin <14 g/dL in men; <12 g/dL in women) was observed in 36%. More severe anemia (hemoglobin

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<11 g/dL in men; <10 g/dL in women) was infrequent, observed in 5% of patients.

The pathogenesis of HIV-related anemia is often complex and multifactorial, including myelosuppressive effects of various drugs (notably zidovudine, co-trimoxazole, and ganciclovir); coinfections; inflammation causing iron utilization defect; HIV infection of marrow stromal cells, which limits their ability to support erythropoiesis; and mild relative EPO deficiency in some patients. Bleeding, autoimmune or drug-induced hemolysis, iron or folate deficiency also may contribute. Risk factors for anemia development include zidovudine use, CD4 lymphocyte count $<0.2 \times 10^9$/L, high HIV viral load, African American ethnicity, and female sex.

Anemia in HIV infection is independently associated with decreased survival, and retrospective analyses suggest that recovery from anemia is associated with decreased risk of death. Although rhEPO therapy has been reported to increase hemoglobin level and reduce transfusions in some patients, there is no evidence that survival is improved as a result of rhEPO therapy.

In early studies, epoetin alfa (100 to 200 U/kg 3 times per week) was reported to significantly improve hemoglobin levels and reduce transfusion requirements in patients with AIDS who were receiving zidovudine, with endogenous plasma EPO level <500 U/L. Epoetin alfa given once per week (40,000 to 60,000 U) for patients with hemoglobin <12 g/dL was reported to be effective in raising hemoglobin level and improving quality of life. Previous studies have not addressed the issue of optimal target hemoglobin in this clinical setting. Caution is advisable given the reported adverse effect profile in CKD and cancer patients associated with targeting normal hemoglobin levels. In the HIV disease setting, the current FDA-approved label indicates to dose epoetin alfa to achieve a hemoglobin level needed to avoid red blood cell transfusions, to withhold therapy if hemoglobin exceeds 12 g/dL, and to discontinue therapy if no increase in hemoglobin is observed at 8 weeks at a dose level of 300 U/kg per week.

Allogeneic blood transfusions in patients undergoing surgery

Perioperative epoetin alfa administration reduces the risk of allogeneic blood transfusions in patients undergoing major elective, nonvascular, noncardiac surgery, primarily studied in the orthopedic surgery setting. The FDA-approved regimens for this indication are 300 U/kg daily subcutaneously for 14 days total, administered daily for 10 days before surgery, on the day of surgery, and for 4 days after surgery. In patients undergoing major orthopedic surgery with pretreatment hemoglobin of 10 to 13 g/dL, significantly fewer epoetin-treated patients (23%) required transfusions compared with a placebo group (45%). In the cohort with baseline hemoglobin of 13 to 15 g/dL, there was no significant difference in the number of patients transfused (9% for epoetin alfa and 13% for placebo). An alternative approved epoetin alfa regimen is 600 U/kg/week subcutaneously administered 21, 14, and 7 days before surgery and on the day of surgery. Consideration of antithrombotic prophylaxis is recommended during perioperative epoetin alfa therapy.

Two modified epoetin alfa regimens were investigated in a randomized, double-blind, placebo-controlled trial involving 201 patients undergoing primary hip arthroplasty with hemoglobin level 9.8 to 13.7 g/dL. Four weekly doses (20,000 or 40,000 U) starting 4 weeks before surgery were administered along with oral iron supplementation. Both epoetin alfa regimens significantly reduced the requirement for allogeneic blood transfusions (22.8% for the low-dose and 11.4% for the high-dose group) compared with the placebo group (44.9%). The incidence of thromboembolic events was not different between groups.

In a trial of 680 patients undergoing spinal surgery who did not receive thromboprophylaxis, patients were randomized to preoperative epoetin alfa 600 U/kg for 4 doses (21, 14, and 7 days prior to surgery and on the day of surgery) or standard care. There was an increased incidence of deep vein thrombosis (4.7%) in the epoetin alfa–treated cohort compared with the standard care patient group (2.1%).

Preoperative epoetin alfa treatment has been used to facilitate autologous blood donation, although routine application for this indication is not justified in clinical practice for reasons of cost and safety; notably, an increased risk of postoperative venous thromboembolism if hemoglobin levels are elevated at the time of surgery. Selected anemic patients who are willing to donate autologous blood or those who decline allogeneic or autologous red blood cell transfusions based on their religious beliefs may benefit from preoperative epoetin therapy. One study randomized patients with mild anemia (hematocrit ≤39%) to treatment with 3 different dosing regimens of epoetin alfa or placebo beginning 25 to 35 days before surgery. Iron supplementation was given intravenously. A dose-dependent increase in the number of autologous units donated was observed.

Other clinical uses of rhEPO

Anemia in patients declining transfusion

The published literature is dotted with small series and case reports discussing the use of erythropoiesis-stimulating

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agents in patients who decline allogeneic or autologous blood transfusion. One such report reviewed the outcomes of 500 Jehovah's Witness patients undergoing cardiac surgery at a single center. This study compared an evolving bloodless surgical strategy in 2 successive eras. In addition to blood-conserving operative techniques, the backbone of this regimen was the administration of epoetin alpha 300 U/kg intravenously, plus 500 U/kg subcutaneously, on admission. After surgery, 500 U/kg was given subcutaneously every second day, along with intravenous iron supplementation. Aminocaproic acid was also given from the time of anesthesia induction to skin closure. For the patients managed with this strategy, the 30-day mortality from the time of surgery ranged from 1% to 3%. Data on thrombotic events was not reported. In light of the risk of venous thromboembolism associated with use of erythropoiesis-stimulating agents in patients with a hemoglobin level over 10 g/dL, as per the FDA's black box warning, it is difficult to reconcile the potential risks and benefits of this approach. The ongoing Transfusion Indication Threshold Reduction 2 (TITRe2, ISRCTN70923932) randomized trial is expected to provide insight into what is an acceptable transfusion threshold in patients undergoing cardiac surgery, the results of which will be directly applicable to the care of Jehovah's Witness and other patients who decline transfusions.

rhEPO have been evaluated in anemia in preterm infants, in ischemic strokes, in anemia in patients suffering of congestive heart failure and in patients in intensive care for severe trauma, but without any positive results on the outcomes.

Myelodysplastic syndromes

Anemia is the most common cytopenia encountered in patients with MDS. rhEPO has been used as monotherapy or in combination with G-CSF for treatment of anemia in MDS. Studies using darbepoetin alfa report erythroid response rates that are comparable to those with epoetin alfa or beta. In March 2017, the European Medicines Agency approved epoetin alfa for the treatment of anemia in lower-risk MDS patients, based on the results from a phase 3 clinical trial and three European registry studies.

The erythroid response rate, reported in single-arm studies, varies widely between 20% and 50% depending on patient selection and the response criteria used. Factors predicting better response rate to therapy include a low transfusion requirement (<2 units/month), low endogenous pretreatment plasma EPO level (<500 U/L), <10% bone marrow blasts, and low/intermediate-1 (int-1) risk International Prognostic Scoring System (IPSS), low flow cytometry score (red score) and higher hepcidin/ferritin ratio reflecting a better iron recirculation. Therefore, rhEPO therapy should be introduced early in the course of the disease in MDS , to avoid transfusion dependence.

The addition of low-dose G-CSF may augment the hemoglobin response to rhEPO therapy, although the role of G-CSF therapy on the biology and course of MDS has not been defined. Meta-analyses have suggested that higher weekly epoetin or darbepoetin doses may elicit better erythroid response rate (epoetin alfa or beta at 60,000 to 80,000/week and darbepoetin alfa at 300μg/week); however, the optimal doses of these agents have not been studied in prospective, randomized studies. Therapy typically is maintained for 12 weeks to assess efficacy and then should be continued until the positive effect on anemia and transfusion requirements is lost (usually after a median of 20-24 months).

No randomized study to date has shown definitively that rhEPO therapy affects the natural course of patients with MDS. Two retrospective studies have reported improved survival in responders to rhEPO therapy compared with nonresponders. The largest retrospective study involved 403 patients with de novo MDS (303 patients IPSS low and int-1 risk). The epoetin alfa or beta regimen was 60,000 U weekly, and darbepoetin alfa was 300 μg weekly for at least 12 weeks. Some patients (33%) also received G-CSF. The erythroid response rate was 40% or 50% using different response assessment criteria. Median duration of response was 20 months from the onset of rhEPO therapy. Compared with a historical, untreated MDS cohort, rates of AML progression were similar. Overall survival was better in rhEPO responders compared with nonresponders or compared with untreated, matched, historical controls. Nevertheless, patients having early loss of response to rhEPO (less than 1 year) will have a higher incidence of AML, suggesting that alternative treatments (luspatercept, ongoing trials with imeltelstat or roxadustat, HIF modulator) should be proposed to these patients.

Adverse effects associated with rhEPO therapy

The safety profile and adverse effects of epoetins and darbepoetin alfa are considered to be comparable. Cardiovascular adverse effects, venous thromboembolism, and increased mortality or tumor progression in cancer patients constitute the major concerns. Pure red cell aplasia due to the development of anti-EPO antibodies is rare and has been described predominantly in patients with CKD.

Cardiovascular adverse effects

rhEPO use may be associated with exacerbation of hypertension, particularly in patients with CKD, and therefore

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therapy should not be initiated in individuals with uncontrolled hypertension. Blood pressure monitoring is essential and avoiding rapid rise of hemoglobin during therapy may ameliorate the risk of hypertension. An increase of blood pressure medication dose may be required during rhEPO therapy. Hypertensive encephalopathy may be associated with a rapid rise in blood pressure. Seizures, usually related to uncontrolled hypertension, rarely may occur.

A series of randomized clinical trials raised concern for worse cardiovascular outcomes and mortality in CKD patients treated with rhEPO to achieve and maintain normal or near-normal hemoglobin levels compared with lower levels. The Normal Hematocrit Trial randomized 1,233 hemodialysis patients with cardiac disease to epoetin alfa therapy to achieve a hematocrit target of 30% or 42%. There was an insignificant trend toward an increase in nonfatal myocardial infarcts or death associated with increased hematocrit, leading to early termination of the study.

In predialysis CKD patients, the CHOIR study involved 1,432 epoetin alfa–treated patients randomized to target a hemoglobin of 13.5 g/dL or 11.3 g/dL. This study was terminated early due to a significant (34%) increase in composite cardiovascular outcome (death, myocardial infarction, hospitalization for congestive heart failure or stroke) in the normal hemoglobin group. Post hoc analyses suggested that failure to achieve the target hemoglobin and a requirement for higher doses of epoetin alfa were associated with increased risk of adverse cardiovascular outcomes.

The TREAT trial randomized 4,038 predialysis CKD patients with diabetes and anemia to treatment with darbepoetin alfa, either to a hemoglobin target of 13 g/dL or to placebo with matching rescue darbepoetin when hemoglobin was <9 g/dL. There was a doubling of the risk of stroke in patients assigned to darbepoetin compared with placebo. It is noteworthy that in the subset of patients with a history of cancer at baseline, significantly more patients died of cancer in the darbepoetin group compared with placebo. In a follow-up analysis of the TREAT trial data, a poor initial response to darbepoetin was associated with an increased subsequent risk of death or cardiovascular events, as doses were escalated to meet target hemoglobin levels.

Venous thromboembolism

In the supportive oncology setting, rhEPO therapy is associated with increased venous thromboembolism risk, observed in both literature-based and individual patient data meta-analyses as well as in randomized controlled trials. The overall rate of these events is relatively infrequent. For instance, a literature-based meta-analysis reported venous thromboembolism in 7.5% of 4,610 patients treated with rhEPO compared with 4.9% of 3,562 control patients (relative risk, 1.57; 95% confidence interval [CI], 1.31-1.87). The mechanisms of venous thromboembolic events are not well defined and a conclusive link between hemoglobin levels and increased thromboembolism risk has not been established. Increased risk of arteriovenous access thrombosis in hemodialysis patients has been reported in association with higher hemoglobin levels.

Mortality or tumor progression in cancer patients

A series of clinical trials since 2003 reported adverse effects, including tumor progression or increased mortality in some rhEPO-treated patients, across a diverse group of malignancies—including lymphoproliferative malignancies and head-neck, breast, non-small-cell lung, uterine cervix, and mixed nonmyeloid cancers. The safety signals in these trials led to implementation of rhEPO use restrictions and REMS to minimize the potential for harm. Four of the 8 trials involved chemotherapy-treated patients, 2 trials included patients treated with radiotherapy only, and 2 trials involved patients with advanced cancer who did not receive antitumor therapy. In all 8 trials, the target hemoglobin level during rhEPO treatment was >12 g/dL, higher than presently recommended. In 2 trials, however, the achieved hemoglobin level was <12 g/dL, therefore raising concern that adverse rhEPO effects may occur at lower hemoglobin levels as well.

An individual patient data meta-analysis evaluating the effect of rhEPO therapy on mortality risk and survival included 53 studies with 13,933 patients. There was a significantly increased mortality risk (hazard ratio: 1.17, 95% CI 1.06-1.30, $P = 0.003$) during the active study period associated with rhEPO therapy. In the subgroup of patients receiving chemotherapy, the observed increase in mortality risk did not reach statistical significance (hazard ratio: 1.10, 95% CI 0.98-1.24, $P = 0.12$). In this meta-analysis, it was not possible to conclusively identify a subgroup of patients with either an increased or decreased mortality risk when receiving rhEPO compared with other patients. rhEPO dosing frequency three or more times a week compared with less frequent schedules (once a week or once every 2 weeks) was associated with reduced mortality, although there were confounding factors in this analysis and a dose-response association was not detected. ESAs may be offered to patients with chemotherapy-associated anemia whose cancer treatment is not curative in intent and whose hemoglobin has declined to <10 g/dL.

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Pure red cell aplasia

Pure red cell aplasia is a rare complication that has been encountered primarily in CKD patients treated with subcutaneous rhEPO and is mediated by neutralizing anti-EPO antibodies that cross-react with endogenous EPO. The peak incidence in 2001 was associated with a change in the formulation of a specific epoetin alfa product (Eprex) containing a new stabilizing agent thought to induce increased immunogenicity of the drug with subcutaneous administration. There have only been rare cases of red cell aplasia after the formulation problem was addressed and Eprex has been administered by an intravenous route.

Loss of rhEPO response during therapy associated with a hemoglobin decline of >0.5 to 1.0 g/dL/week and low reticulocyte count ($<10 \times 10^9$/L) leads to clinical suspicion of red cell aplasia. Bone marrow examination reveals absent or severely reduced erythroid precursor cells. Serum EPO antibody testing is required to confirm diagnosis. Discontinuation of drug is indicated. Hematologic recovery occurs in the majority of patients treated with immunosuppressive therapy, such as corticosteroids, daily oral cyclophosphamide, calcineurin inhibitors, or rituximab. Peginesatide, a novel EPOR agonist that does not cross-react with EPO antibodies, has been used successfully in the treatment of some patients. However, this was removed from the US market in 2013 because of increased deaths and cardiovascular events.

Blood doping in sports

There is an extensive literature about athletes using recombinant EPO to improve performance in sports. In the 1980s, some athletes began to transfuse their own blood back into themselves prior to events. Once this was found to help athletic performance, alternative strategies to increase the hemoglobin were sought. When recombinant EPO became available, many capitalized on its availability to raise hemoglobin and increase VO_2 max. Some participants in endurance sports (such as cycling, rowing, long-distance running, cross-country skiing, and triathlon) started using EPO. By increasing the hematocrit, it was thought, improvement in oxygen delivery to the muscles would improve endurance. Rules governing the use of EPO in this setting were promulgated, and athletes would try to circumvent these rules by adopting the use of EPO agents, which could not be detected by laboratories at that time. Great controversy clouded sports such as cycling, and legendary athletes have had their reputations tarnished by discovery of their doping.

In 2017, a provocative update to the blood doping story occurred. Heuberger and colleagues performed the first randomized double-blind trial in which erythropoietin or matched placebo was administered to well-trained cyclists. The study was small and included just 48 participants: 24 to EPO and 24 to placebo. EPO increased the mean hemoglobin concentration from 9.0 to 9.6 mmol/L. EPO increased the maximal power output and VO_2 max, though submaximal parameters, including the mean power output and mean VO_2 consumption, were unchanged. Finally, race times during a day of climbing were no different between groups. The authors conclude that "the more clinically relevant submaximal exercise test performance and road race performance were not affected. This study shows that clinical studies with doping substances can be done adequately and safely and are relevant in determining effects of alleged performance-enhancing drugs."

rhEPO biosimilars and other erythropoiesis-stimulating agents

The rationale for the development of epoetin biosimilars is cost saving. These products are not fully identical to the original drugs (165 amino-acid epoetin but they are differently glycosylated and the difference in glycosylation gives the greak suffix alfa, zeta ot theta). Documentation of their quality, safety, and efficacy is essential. Immunogenicity and the production of autoantibodies induced by biosimilar epoetins have been associated with pure red cell aplasia. Approved epoetin biosimilars are available for clinical use in Europe, especially for epoetin alfa and epetin zeta.

A novel class of erythropoiesis-stimulating agents in clinical development involves HIF stabilization by pharmacologic inhibition of the prolyl hydroxylation of HIF—the transcription factor that controls EPO gene expression—thereby preventing its degradation in the proteasome. An orally bioavailable prolyl hydroxylase domain inhibitor, FG-2216, was reported to increase the plasma EPO level in end-stage renal disease patients (even in anephric hemodialysis patients), suggesting that abnormal oxygen sensing—not a loss of EPO production capacity—plays a role in renal anemia. It is currently in clinical trial in myelodysplastic syndromes.

Platelet growth factors

Thrombopoietin

TPO is the major growth factor that regulates megakaryopoiesis and platelet production. TPO is constitutively synthesized, primarily in the liver. The TPO receptor, MPL (myeloproliferative leukemia virus oncogene), is expressed on megakaryocytes and platelets. The current paradigm is

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that the level of TPO available to bind to megakaryocytes is inversely related to the platelet number; ie, the lower the platelet count, the higher the level of free TPO, the more binding to MPL on megakaryocytes, and the greater the level of platelet production. TPO-activate MPL activates JAK2 tyrosine kinase and downstream intracellular signaling (see video in online edition). The disruption in mice of the gene encoding either TPO or MPL leads to severe thrombocytopenia due to reduced number of megakaryocytes.

Congenital amegakaryocytic thrombocytopenia (CAMT) may be associated with elevated serum TPO levels, due to lack of receptor-mediated uptake. Pecci et al have described mutations in thrombopoietin in some patients with CAMT. Naturally occurring mutations in the gene encoding TPO that lead to increased plasma TPO levels have been found in families with hereditary thrombocytosis. Gain-of-function mutations in the *MPL* gene also have been reported as the basis for congenital or inherited thrombocytosis. Acquired, somatic mutations *MPL* W515L/K have been found in 5% to 10% of patients with essential thrombocytosis and primary myelofibrosis. Homozygous or compound heterozygous inactivating mutations in *MPL* have been reported in association with decreased TPO response in congenital amegakaryocytic thrombocytopenia.

TPO receptor agonists

The development of therapeutic agents to stimulate thrombopoiesis has been of great interest to treat severe thrombocytopenia and bleeding associated with common hematologic conditions, such as chemotherapy-induced thrombocytopenia (CIT), MDS, and immune thrombocytopenia (ITP). First-generation recombinant TPOs were investigated in clinical trials involving healthy individuals and patients with chemotherapy-induced thrombocytopenia. In studies with pegylated recombinant human megakaryocyte growth and development factor (PEG-rHuMGDF) PEG-rHuMGDF, antibodies that cross-reacted with endogenous TPO developed in some recipients. Antibodies were not observed with recombinant human thrombopoietin (rhTPO), however, development of both recombinant forms was discontinued in most countries. rhTPO is currently produced and available in China.

Second-generation agents, termed TPO receptor agonists (or TPO-RA), have now been developed that mimic the effect of endogenous TPO, by binding to and activating the TPO receptor, promoting megakaryocyte growth, differentiation, and platelet production. Several TPO-RA have now been developed. Romiplostim is a fusion protein of a 14 amino acid sequence that binds to the extracellular domain of the MPL, conjugated to the Fc region of a human IgG1 antibody. Of note, the amino acid sequence of the MPL-binding domain of romiplostim does not contain sequence from endogenous TPO. Eltrombopag, avatrombopag, and lusutrombopag are orally available small molecules that bind to the transmembrane portion of the receptor. The initial approval and therapeutic use of TPO-RAs (romiplostim, eltrombopag, and avatrombopag) was for chronic ITP. Eltrombopag is also approved for severe aplastic anemia (SAA) and hepatitis C-associated thrombocytopenia (Table 4-9). Lusutrombopag and avatrombopag are FDA-approved for treatment of adult patients with thrombocytopenia on the basis of chronic liver disease scheduled to undergo a procedure.

TPO receptor agonists in ITP

The TPO-RA are approved for chronic ITP, as second line therapy, in general for patients who have had insufficient response to glucocorticoids or other first-line therapy. The TPO-RA have become a well established therapy for chronic ITP as they are well tolerated and effective, and do not involve alteration of the immune system. Doses are easily titrated to maintain a stable platelet count of $\geq 50 \times 10^9$/L, as necessary to reduce the risk for bleeding.

Randomized placebo-controlled trials of romiplostim involving splenectomized and nonsplenectomized patients with ITP have demonstrated that romiplostim leads to a durable platelet response in splenectomized and nonsplenectomized patients with chronic ITP. The approved initial dose of romiplostim is 1 μg/kg as a weekly subcutaneous injection with dose titration to maintain a stable platelet count of $\geq 50 \times 10^9$/L, as necessary to reduce the risk for bleeding by using the lowest dose of romiplostim. However, real world experience supports starting treatment with a higher dose, typically 2 μg/kg. The maximum weekly dose is 10 μg/kg. The development of romiplostim-binding antibodies is rare, and these antibodies are not cross-reactive with TPO.

Table 4-9 FDA-approved indications for romiplostim and eltrombopag

Thrombocytopenia due to:
Chronic ITP in adults with an insufficient response to corticosteroids, immunoglobulins, or splenectomy (romiplostim and eltrombopag); and in adults and children as young as 1 year old (eltrombopag only), though studies of romiplostim in pediatric patients with ITP have been completed
Chronic hepatitis C to allow the initiation and maintenance of interferon-based therapy (eltrombopag only)
Severe aplastic anemia with an insufficient response to immunosuppressive therapy (eltrombopag only)

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Eltrombopag (50 mg once daily as usual starting dose) is effective in treatment of chronic ITP. Platelet counts of ≥50 × 10^9/L at 6 weeks were achieved in 59% of eltrombopag-treated patients compared with 16% of placebo-treated patients. Eltrombopag use has multiple dietary interactions, reducing its potential utlility in cancer patients. Eltrombopag needs to be taken at least 2 hours before or 4 hours after any medications or products containing polyvalent cations, such as antacids, calcium-rich foods, and mineral supplements. Dietary fat reduces its oral bioavailability. And eltrombopag is a potent iron chelator and may adversely impact iron stores. Patients with moderate to severe hepatic impairment (Child-Pugh score >7) and individuals of East Asian ethnicity should be started on a lower dose. Eltrombopag doses should be titrated toward the target platelet level of ≥50 × 10^9/L. The daily dose should not exceed 75 mg.

Avatrombopag (20 mg once daily as usual dose) is a second oral TPO-RA FDA approved for treatment of chronic ITP. In a phase 3 trial of avatrombopag versus placebo, avatrombopag was superior to placebo in the median cumulative enumber of weeks of platelet response, and there was a significant improvement in platelet count by day 8 (65.63% versus 0.0%; $P < 0.0001$). Avatrombopag should be taken with food, and does not interactions with cation-rich foods or supplmenents.

TPO-RA should not be used in an attempt to normalize platelet counts. Platelet counts should be measured weekly until stable at ≥50 × 10^9/L for at least 4 weeks without dose adjustment, and then monthly thereafter. Dose reduction is recommended when platelets are >200 × 10^9/L. Rebound thrombocytopenia after drug discontinuation, characterized by a transient worsening of thrombocytopenia 10 × 10^9/L below the pretreatment baseline, may occur in 8% to 10% of patients, and may be associated with increased risk of bleeding. If treatment is held or discontinued, it is advisable to monitor platelet counts twice a week for at least 2 weeks and reinitiate other treatments as indicated. Platelet counts usually recover to baseline after several weeks.

Adverse effects of TPO-RA are infrequent, but include headache, nausea, vomiting, diarrhea, fatigue, nasopharyngitis, and arthralgia. Eltrombopag may be associated with hepatic injury and elevated alanine aminotransferase levels, observed in 10% of patients compared with 7% to 8% of placebo in clinical trials. Serum liver enzymes should be checked before initiation of eltrombopag therapy, every 2 weeks during the dose titration period, and then monthly after establishment of stable dose.

A possible increased risk for arterial or venous thromboembolism (approximately 6%), emerged in long-term studies of TPO-RA treatment of ITP. However, there was no control arm in the extension studies and ITP itself is known to be associated with an increased risk of thrombosis. These limitations prevent clear conclusion on the magnitude of thrombotic risk, if any, with treatment of a TPO-RA for ITP. Possible increased risk, awaits confirmation in "properly designed trials."

Development of of increased bone marrow reticulin deposition and fibrosis was reported in early studies of TPO-RA. With further study and experience, bone marrow reticulin deposition and fibrosis appears to be infrequent and reversible following discontinuation of therapy. This usually occurred in patients receiving higher doses and/or longer-term exposure to the TPO-RA. While on long-term therapy, periodic monitoring for the development of anemia and leukoerythroblastic changes in peripheral blood is advisable.

TPO receptor agonists in aplastic anemia

Eltrombopag has been shown to be effective, and is now FDA approved for treatment of SAA. In a notable phase 1/2 study, of previously untreated patients with severe aplastic anemia, addition of daily eltrombopag to conventional immunotherapy, resulted in complete response in 58% or patients and overall response rates at 6 months of 94%. A key observation was that eltrombopag improved neutrophils and red cells, not only platelets. Eltrombopag is indicated for patients with SAA, in first-line in combination with standard immunosuppressive therapy and for patients who have had an insufficient response to immunosuppressive therapy.

Thrombocytopenia in chronic liver disease: prior to surgery

Thrombocytopenia is a common manifestation of chronic liver disease and TPO-RA have been evaluated in this setting. For patients with chronic liver disease and thrombocytopenia undergoing invasive procedures, avatrombopag and lusutrombopag have been shown to be effective in improving platelet counts prior to planned surgery and reducing the need for platelet transfusions. There was no significant increase in thrombotic events compared with placebo. Both avatrombopag and lusutrombopag are now approved for treatment of thrombocytopenia in adult patients with chronic liver disease who are scheduled to undergo a procedure. These TPO-RA need to be started over a week prior to the procedure, limiting their use to nonurgent procedures.

Eltrombopag was studied in the same setting, patients with chronic liver disease 14 days before an invasive elective procedure. This trial was terminated because of the

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occurrence of portal vein thrombosis in 6 patients of the eltrombopag group (n = 145), compared with 1 patient in the placebo group (n = 147).

In a case series, romiplostim has also been shown to improve platelet counts when started 1-2 weeks before the procedure, allowing surgery to proceed on schedule in 96% of the treated patients.

Thrombocytopenia in chronic liver disease

Eltrombopag was investigated in a randomized placebo-controlled trial for the treatment of thrombocytopenia associated with hepatitis C–related cirrhosis to facilitate antiviral therapy by improving platelet counts. It was effective in allowing for the initiation of antiviral therapy and was well tolerated during the 20-week treatment period. The current FDA approval specifies eltrombopag use in patients with chronic hepatitis C whose degree of thrombocytopenia prevents the initiation of interferon- based therapy or limits the ability to maintain interferon-based therapy. However, interferon is no longed used routinely to treat hepatitis C.

Myelodysplastic syndromes

A potential role for TPO-RA in treatment of MDS remains unresolved. Eltrombopag and romiplostim have been studied in lower-risk MDS. In a phase 1/2 trial that involved 44 patients with lower-risk MDS and platelets ≤50 × 10^9/L, treatment with single agent weekly romiplostim was associated with a 46% platelet response and reduced bleeding. While an initial signal of possible increased risk of progression to leukemia led to termination of the study a subsequent 5-year follow-up analysis did not confirm an increased risk of AML and the authors concluded "that use of romiplostim is probably not associated with any increased risk of acute myeloid leukaemia or death, despite initial concerns."

A study of eltrombopag in low to intermediate risk-1 MDS showed a 44% hematopoietic response. Of the 25 eltrombopag-treated patients, 3 patients developed reversible grade-3 liver toxicity and 1 patient had increased reticulin fibrosis. In contrast, a separate phase 3 study of intermediate–high-risk MDS treated with azacytidine compared eltrombopag with placebo. The study was terminated early due to inferiority; 16% of eltrombopag-treated patients achieved transfusion-free status compared with 31% of placebo control patients.

While data supporting a possible adverse risk with TPO use in MDS is not strong, this concern has led to explicit FDA-mandated language that romiplostim and eltrombopag are not indicated for the treatment of thrombocytopenia due to MDS.

TPO receptor agonists for chemotherapy-induced thrombocytopenia

Thrombocytopenia occurs frequently in cancer patients, resulting from cytotoxic and targeted chemotherapy. In addition, bone marrow metastasis, radiation therapy, and comorbidities may also contribute to thrombocytopenia. Since the liver is the site of TPO production, primary or metastatic cancer involvement of the liver also may contribute to thrombocytopenia. Chemotherapy-induced thrombocytopenia is the most common etiology. CIT can contribute to morbidity and mortality through bleeding complications but this is relatively uncommon. The primary impact of CIT is that it leads to delay and/or dose reduction in chemotherapy, referred to as reduced relative dose intensity of chemotherapy.

A number of early stage clinical trials have been published on use of TPO-RA for prevention and treatment of CIT, showing efficacy. The most mature data for use of a TPO-RA for treatment of CIT is with romiplostim. In two studies, romiplostim has been shown to correct CIT in over 70% of patients, significantly reduce the recurrence of CIT and reduce the need for platelet transfusion. In a phase 2 study of patients treated with gemcitabine-based chemotherapy, eltrombopag shortened the time to recovery from platelet nadir and reduced dose delays/reductions due to thrombocytopenia. It should be noted that this was not a trial of established CIT. The current NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Hematopoietic Growth Factors (version 1.2022) endorse consideration of romiplostim as an option for treatment of CIT based on level 2A evidence. However, neither romiplostim nor other TPO-RA are currently approved by the Food and Drug Administration for treatment or prevention of CIT.

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